AstraZeneca

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **ROBERTS ET AL.**	Filed: **November 17, 2003**
Application No: **10/714,447**	Attorney Docket No.: **A1479-3P US**
Art Unit: **1624**	Examiner: **Emily Bernhardt**
Title: **Novel Compounds with Analgesic Effects**	

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REPLY BRIEF PURSUANT TO 37 CFR 41.41

Applicants are filing this Reply Brief as a matter of right, pursuant to 37 CFR § 41.41(a)(1), within two months of the April 18, 2008 mailing date of the Examiner's Answer. No fees are believed due for the submission of this Reply Brief. If, however, any additional fees are due, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 26-0166, referencing Attorney Docket No. A1479-3P.

ARGUMENT

Claim 19 stands rejected under 35 U.S.C. § 103 (a) as being obvious over Calderon et al. and the Bilsky et al. references in view of Chang et al. (PCT Publication WO93/15062 or U.S. Pat. No. 5,658,908, applied as of its § 102(e) date).

The Examiner continues to erroneously assert in the Examiner's Answer mailed April 18, 2003 (hereinafter the "Answer") that Chang et al. teaches methyl and hydrogen groups are equivalent and therefore it would have been obvious to a person of ordinary skill in the art to exchange the methyl groups contained on the central piperazine ring of the Bilsky et al. and Calderon et al. compounds with the hydrogen groups disclosed in Chang et al. More precisely, the Examiner concedes that "compounds in the primary reference are no longer anticipatory in view of the … presence of only hydrogen on piperazino carbons" (see page 5 of Answer) (emphasis added) but goes on to assert the presently claimed compounds are obvious variants over the Calderon et al. and Bilsky et al. compounds because Chang et al. indicates methyl and hydrogen are equivalent. For example, the Examiner asserts at page 5 of the Answer that "the compounds in the primary references are obvious variants of that still claimed herein since the differences allyl vs instant R1 as H, alkyl, aralkyl etc. are taught as interchangeable as well as

methyl and hydrogen on piperazino compounds in similar compounds having the same use as described by the Chang patent." In short, the Examiner is relying on Chang et al. to make up for the hydrogen groups she openly admits are missing from the Bilsky et al. and Calderon et al. central piperazine ring.

Applicants, however, have scoured the Bilsky et al. and Calderon et al. references and note, as acknowledged by the Examiner, that none of the references indicate the methyl groups contained on the central piperazine ring of the compounds disclosed therein can be successfully exchanged for hydrogens. In fact, although these references stress the importance of the stereochemistry associated with a di-methylated central piperazine ring and the benzylic carbon of the compounds disclosed therein, none of these references mention 1) a single compound having only hydrogen groups substituted on the central piperazine ring, 2) how exchanging the central piperazine methyl groups with hydrogen groups will affect the activity of such compounds, and/or 3) what the activity will/might be for compounds containing such a hydrogen modified central piperazine ring.

Furthermore, the Examiner misinterprets Applicants' comments regarding the central piperazine ring of Chang et al. Specifically, Applicants' argued at page 7 of their Brief filed December 3, 2007, that Chang et al. expressly stated during the prosecution of the '908 patent that methyl and hydrogen did not behave equivalently and therefore were not readily interchangeable. Applicants further indicated at page 7 of their Brief that Chang et al. stated in relevant part in reliance on a 132 declaration as follows:

> Specifically, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring. The test results, *comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity*. (Emphasis added).

In the Answer, the Examiner responded at page 8 as follows:

> The declaration presented in Chang was a comparative showing between prior art and relevant compounds of Chang that are totally dissimilar to that shown as obvious herein. There is no carboxamide substituent on the phenyl ring always required herein. The quote in the Declaration and elsewhere in Chang's remarks appellants heavily rely on as showing a general trend of better activity when at least one methyl group is present, is noted, but is believed to be taken out of context and its significance to the present claimed subject matter exaggerated given the homogeneity of the tested examples along with their dissimilarity to the compounds on appeal herein. Thus it is not seen how the declaration in Chang mitigates its teachings as a reference."

Applicants point, however, is that Chang et al. expressly indicated during prosecution that a central piperazine ring having all hydrogens substituted thereon will not have the "significantly greater opioid activity" of compounds containing a methyl substituted central piperazine ring. Chang et al.'s own statements indicate a person of ordinary skill in the art did not believe at the time the presently claimed invention was filed that hydrogen and methyl behaved equivalently.

Moreover, Applicants disagree with the Examiner's assertion that Chang et al.'s comments have been taken out of context. In fact, Applicants regard the presence of the piperazine ring in the compounds Chang et al. referred to in characterizing the comparative data discussed during prosecution of Chang et al. to be the most relevant aspect of Chang et al.'s comments. The Examiner appears to want to have it both ways. The Examiner wants Chang et al. to teach hydrogen and methyl are equivalent across the scope of what Chang et al. discloses but also wants Chang et al.'s own comments indicating hydrogen and methyl do not behave equivalently across the scope of what Chang et al. discloses to be ignored. The Examiner, however, cannot have it both ways.

Chang et al.'s remarks, regardless of what other substituent groups may be present on compounds containing a piperazine core, indicate it is difficult to predict what impact a hydrogen-methyl exchange will have on the delta activity of the resulting piperazine derivative. This unpredictability is evidenced by the fact that hydrogen and methyl did not behave equivalently in the compounds for which Chang et al. provided comparative data, and therefore there would have been no reason for a person of ordinary skill in the art to believe hydrogen and methyl would behave equivalently in any other piperazine derivatives.

Furthermore, Applicants statement regarding the ***Exemplified*** compounds of Chang et al. is accurate. While there may be compounds disclosed in the specification of Chang et al. lacking any methyl groups on the central piperazinyl ring, Applicants assert Chang et al.'s failure to include such compounds in the Example section or within the scope of the broadest claim further supports Chang et al.'s own statements that hydrogen and methyl are not equivalent.

As a result, and in contrast to what the Examiner would like one to believe, methyl and hydrogen are not equivalent and therefore a person of ordinary skill in the art would not have been motivated to replace the methyl groups substituted on the central piperazine ring of the Bilsky et al. and Calderon et al. compounds with the hydrogen groups needed to arrive at Applicants' claimed invention.

CONCLUSION

In view of at least the unpredictability of how opioid receptor activity would be impacted by a hydrogen-methyl exchange, Applicants' respectfully assert the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully urge the Board to find the invention of claim 19 is not obvious over the Calderon et al. and Bilsky et al. references in view of Chang et al., and therefore the rejection of Claim 19 pursuant to 35 USC § 103(a) is improper and should be withdrawn.

Respectfully submitted,

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